

(FILE 'HOME' ENTERED AT 14:51:34 ON 03 OCT 2003)

FILE 'USPATFULL' ENTERED AT 14:51:44 ON 03 OCT 2003

L1 0 S 6495601/PN  
L2 1 S US6495601/PN  
E COTRANSPORTER ANTAGONIST/CT

FILE 'MEDLINE' ENTERED AT 14:53:26 ON 03 OCT 2003

E COTRANSPORTER ANTAGONIST/CT  
E E6+ALL

FILE 'CAPLUS, MEDLINE, BIOSIS, EMBASE, USPATFULL, JAPIO' ENTERED AT  
14:54:38 ON 03 OCT 2003

L3 2778 S SODIUM-POTASSIUM-CHLORIDE SYMPORTERS OR SODIUM-POTASSIUM-CHLO  
L4 133279 S FUROSEMIDE OR DIURETICS OR THIAZIDE OR HYDROCHLOROTHIAZIDE  
L5 763515 S MIGRAINE OR HEADACHE OR DEPRESSION  
L6 30 S L3 AND L5  
L7 5340 S L4 AND L5  
L8 26 DUP REM L6 (4 DUPLICATES REMOVED)  
L9 26 FOCUS L8 1-

FILE 'REGISTRY' ENTERED AT 15:00:43 ON 03 OCT 2003

L10 20 S FUROSEMIDE

FILE 'CAPLUS, MEDLINE, BIOSIS, EMBASE, USPATFULL, JAPIO' ENTERED AT  
15:01:38 ON 03 OCT 2003

L11 0 S L7 AND 5431-9/RN  
L12 110 S L7 AND 54-31-9/RN  
L13 106 DUP REM L12 (4 DUPLICATES REMOVED)  
L14 106 FOCUS L13 1-

=>

CCESSION NUMBER: 1991:240451 CAPLUS  
DOCUMENT NUMBER: 114:240451  
TITLE: Pharmacological blockade of chloride pumps or Cl-  
channels reduces the adenosine-mediated  
**depression** of stimulus train-evoked calcium  
fluxes in rat hippocampal slices  
AUTHOR(S): Schubert, Peter; Ferroni, Stefano; Mager, Ralph  
CORPORATE SOURCE: Dep. Neuromorphol., Max-Planck-Inst. Psychiatry,  
Martinsried, 8033, Germany  
SOURCE: Neuroscience Letters (1991), 124(2), 174-7  
CODEN: NELED5; ISSN: 0304-3940  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
AB Stimulus train-evoked decreases of the extracellular Ca<sup>2+</sup> concn.  
(.DELTA.Ca) were measured with ion-sensitive electrodes in the CA1 area of  
rat hippocampal slices. The adenosine receptor antagonist theophylline  
led to a marked increase of .DELTA.Ca in the synaptic and in the soma  
layer reflecting an increased activation and enhanced frequency  
potentiation of pyramidal neurons in the absence of endogenous adenosine  
action. The theophylline effect was reduced in the presence of the Cl-  
channel blocker 4,4'-diisothiocyano-2,2'-stilbenedisulfonate (DIDS) or of  
the Cl- pump blocker **furosemide**. The data indicate that the  
adenosine-mediated modulation of the repetitive input strength is related  
to the function of Cl- ions.

ACCESSION NUMBER: 1969:36337 CAPLUS

DOCUMENT NUMBER: 70:36337

TITLE: Physiological observations on the exocrine pancreas.  
Effects of some agents on pancreatic secretion

AUTHOR(S): Nakano, Satoshi

CORPORATE SOURCE: Sch. Med., Nagoya Univ., Nagoya, Japan

SOURCE: Nagoya Journal of Medical Science (1968), 31(1),  
79-116

CODEN: NJMSAG; ISSN: 0027-7622

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Pancreatic secretion studies were performed in dogs and cats under general anesthesia. Pancreatic secretion was maintained by administration of secretin. Following i.v. injection of a synthesized tetrapeptide (I) structurally related to an active part of gastrin a substantial increase of amylase concn. and in amylase output was observed, without any significant change in the other components of the pancreatic juice including electrolytes. Increase in pancreatic juice flow was observed in dogs but not in cats. In human subjects s.c. injection of 300 .mu.g. I after the pancreozymin-secretin combined test resulted in increased juice flow and amylase activity. Injection of serotonin creatinine sulfate (II) resulted in transient **depression** of the juice flow. In dogs the protein content of pancreatic juice increased immediately, but in cats it was either decreased or variable. Hyperventilation and increased motility of the duodenum occurred. In rats multiple gastric ulcers were produced by II. Significant increase of amylase concn. and output in both cats and dogs followed neostigmine administration. There were no significant changes of juice flow or bicarbonate concn. Atropine sulfate did not affect the pancreatic juice flow but inhibited the enhancement of amylase activity by neostigmine. Administration of hyoscine N-butyl bromide (III), a ganglionic blocking agent, was followed by a significant though transient **depression** of pancreatic juice flow. Amylase concn. was slightly increased but amylase output was depressed. In 2 normal human subjects i.v. injection of III resulted in a marked **depression** in juice flow with decrease in amylase activity in one case and a transient **depression** of juice flow without change in amylase activity in the other. Acetazolamide greatly depressed the pancreatic juice flow with a slight **depression** of bicarbonate concn. and an increase in enzyme concn. Na concn. was unchanged but there was a tendency for K concn. to increase. **Furosemide** injection caused a slight **depression** of juice flow and bicarbonate concn. with a slight elevation of protein concn. and a tendency for K concn. to decrease. Following the pancreozymin-secretin combined test, the administration of **furosemide** caused a **depression** of juice flow and elevation of amylase concn. in a normal subject and a slight elevation of amylase concn. in a patient with chronic pancreatitis.

14 ANSWER 33 OF 106 CAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1967:63866 CAPLUS  
DOCUMENT NUMBER: 66:63866  
TITLE: Diuretic therapy of acute intoxication with hypnotics  
AUTHOR(S): Krueger, G. A.  
CORPORATE SOURCE: Evangelischen Krankenhauses, Muelheim, Fed. Rep. Ger.  
SOURCE: Anaesthetist (1967), 16(2), 40-4  
CODEN: ANATAE; ISSN: 0003-2417  
DOCUMENT TYPE: Journal  
LANGUAGE: German

AB **Furosemide** (20 mg.), injected i.v. into patients with barbiturate intoxication and added to running infusions dependent on the progress of the case (an av. of 20 mg./1000 ml.), was an effective therapeutic measure against the intoxication. The drug was easily administered and could be safely used in case of diabetes or complications caused by **depression** of cardiac, circulatory, or liver functions. It considerably reduced the time of unconsciousness and hospital treatment. Circulatory analeptics, particularly ethyldiphenylpropenamine, were effectively used in cases of hypotension in order to reestablish normal blood pressure values. 46 references.

ACCESSION NUMBER: 1971:517014 CAPLUS

DOCUMENT NUMBER: 75:117014

TITLE: Oxygen consumption and changes of tissue cation concentrations in K<sup>+</sup>-depleted rabbit kidney slices, under the influence of diuretic agents, p-chloromercuribenzoate and N-ethylmaleimide

AUTHOR(S): Herms, W.; Kersting, F.

CORPORATE SOURCE: I. Med. Klin., Univ. Duesseldorf, Duesseldorf, Fed. Rep. Ger.

SOURCE: Progr. Nephrol., Proc. Symp. "Ges. Nephrol.", 5th (1969), Meeting Date 1967, 290-5. Editor(s): Peters, Georges. Springer: Berlin, Ger.

CODEN: 23QNA2

DOCUMENT TYPE: Conference

LANGUAGE: English

AB Incubation of rabbit kidney slices with the diuretic agents mersalyl, **hydrochlorothiazide**, **furosemide**, and ethacrynic acid resulted in decreased tissue respiration and increased K<sup>+</sup> uptake. The absence of a relationship, however, suggests that active K<sup>+</sup> uptake is not closely linked to respiration. An increase in Na<sup>+</sup> concn. which did not parallel the **depression** in K<sup>+</sup> uptake was also obsd. It is possible that cell membrane permeability might be affected by these agents. Addn. of cysteine chloride partially reversed the effects. A greater protective effect was obsd., however, when the nondiuretic agents, p-chloromercuribenzoate and N-ethyl-maleimide were used.

L14 ANSWER 22 OF 106 CAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1971:486492 CAPLUS

DOCUMENT NUMBER: 75:86492

TITLE: Renal and extrarenal factors involved in the hyperuricemia induced by **furosemide**

AUTHOR(S): Schirmeister, J.; Man, N. K.; Hallauer, W.

CORPORATE SOURCE: Med. Universitaetsklin., Freiburg/Br., Fed. Rep. Ger.

SOURCE: Progr. Nephrol., Proc. Symp. "Ges. Nephrol.", 5th (1969), Meeting Date 1967, 59-63. Editor(s): Peters, Georges. Springer: Berlin, Ger.

CODEN: 23QNA2

DOCUMENT TYPE: Conference

LANGUAGE: English

AB Studies were carried out in order to define the renal and extrarenal factors by which **furosemide** modifies the serum uric acid (SUA) concn. The renal effect of **furosemide** in man appears to be 2-fold. First an initial small decrease of urinary urate excretion which could be due to an increased proximal tubular reabsorption of uric acid, enhanced by an increased blood lactate. It is suggested that the 2nd renal effect could be a **depression** of tubular secretion of urate which abolishes the increase in uric acid excretion, expected as a consequence of the augmented uric acid load.

L14 ANSWER 23 OF 106 CAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1976:586781 CAPLUS

DOCUMENT NUMBER: 85:186781

TITLE: Bumetanide, a new loop diuretic

AUTHOR(S): Carriere, S.; Dandavino, R.; Rochefort, F.;

Daigneault, A.; Lanoix, C.

CORPORATE SOURCE: Dep. Med., Hop. Maisonneuve-Rosemont, Montreal, QC, Can.

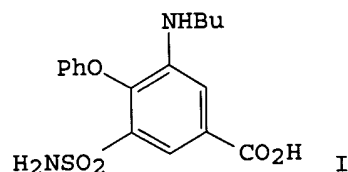
SOURCE: Clinical Pharmacology & Therapeutics (St. Louis, MO, United States) (1976), 20(4), 424-38

CODEN: CLPTAT; ISSN: 0009-9236

DOCUMENT TYPE: Journal

LANGUAGE: English

GI



AB The effect of bumetanide (I) [28395-03-1] on renal function was compared with that of **furosemide** [54-31-9] and a placebo in a double-blind study in 9 healthy young men. The sequence for oral administration of the drug was subjected to a random assignation based upon the Latin-square methodology under these different conditions. During normal hydration the administration of I (2 mg) produced within the next 4 hr a diuresis comparable to that induced by 80 mg of **furosemide**. Urinary excretion of Na, K, Cl, Ca, and uric acid also followed comparable patterns. Phosphaturia occurred only under I. The effect of I seemed longer lasting. During water loading the effects of I and **furosemide** were comparable with the exception of the phosphaturic effect induced by I. The action of both **diuretics** on the diluting segment of the nephron was well demonstrated by the marked **depression** of max. free-water clearance. During water deprivation the effects of the 2 **diuretics** were comparable, including **depression** of max. free-water reabsorption. In none of these

conditions did the placebo produce any significant effect.

L14 ANSWER 24 OF 106 CAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1985:553514 CAPLUS

DOCUMENT NUMBER: 103:153514

TITLE: Nitrogen mustard interference with potassium transport systems in Ehrlich ascites tumor cells

AUTHOR(S): Doppler, Wolfgang; Hofmann, Johann; Oberhuber, Hermann; Maly, Karl; Grunicke, Hans

CORPORATE SOURCE: Inst. Med. Chem. Biochem., Univ. Innsbruck, Innsbruck, A-6020, Austria

SOURCE: Journal of Cancer Research and Clinical Oncology (1985), 110(1), 35-41

CODEN: JCROD7; ISSN: 0171-5216

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Nitrogen mustard (N-mustard) [55-86-7] inhibits ouabain [630-60-4]- and **furosemide** [54-31-9]-sensitive Rb uptake of Ehrlich ascites tumor cells, whereas the Rb transport resistant to both inhibitors is not affected. Rb transport kinetics served as a congener for the K<sup>+</sup>-transport in these cells. At N-mustard concns. <10  $\mu$ M, the redn. in Rb uptake is predominantly due to an interference with the **furosemide**-sensitive system. The dose response curve for the inhibition by N-mustard of the **furosemide**-sensitive Rb uptake closely parallels the dose response curve for the antitumor activity of the alkylating drug. This is in contrast to the behavior of the ouabain-sensitive Rb transport. The inhibition of the **furosemide**-sensitive Rb uptake is expressed much less in cells which are resistant to N-mustard. The recovery of the **furosemide**-sensitive transport system after a single exposure to N-mustard is relatively slow and characterized to an initial 4 h lag period, whereas the repair of DNA-interstrand crosslinks starts immediately after removal of the drug. At millimolar concns., **furosemide** blocks the multiplication of Ehrlich ascites tumor cells. However, lower concns. of **furosemide** which cause a 50% redn. in the **furosemide**-sensitive Rb uptake do not interfere with cell proliferation. This is in contrast to the behavior of N-mustard which exerts a clear-cut **depression** of cell growth at concns. leading to a 50% inhibition of the **furosemide**-sensitive Rb transport transport. It is concluded, that the inhibition of the **furosemide**-sensitive system alone is not sufficient to explain the antitumor activity of the alkylating agent. The effect is discussed as part of a more extended N-mustard-induced membrane alteration which may be important for the growth inhibitory effect of the alkylating agent.

L14 ANSWER 21 OF 106 CAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1976:12436 CAPLUS

DOCUMENT NUMBER: 84:12436

TITLE: Cochlear N1 **depression** produced by the new loop diuretic, bumetanide, in cats

AUTHOR(S): Brown, R. D.

CORPORATE SOURCE: Med. Cent., Louisiana State Univ., Shreveport, LA, USA

SOURCE: Neuropharmacology (1975), 14(8), 547-53

CODEN: NEPHBW; ISSN: 0028-3908

DOCUMENT TYPE: Journal

LANGUAGE: English

AB There was a linear relation between bumetanide (I) [28395-03-1] (1-50 mg/kg, i.v.) and cochlear N1 **depression** in 22 cats. Statistics showed the dose-response curve for I was parallel with other ototoxic **diuretics** and suggested they were acting on the same cochlear sites by the same mechanism. I had an abs. diuretic potency 40-60 times and abs. ototoxic potency .apprx.6.5 times that of **furosemide** (11.92 mg/kg, i.v.).

L14 ANSWER 22 OF 106 CAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1971:486492 CAPLUS

DOCUMENT NUMBER: 75:86492

TITLE: Renal and extrarenal factors involved in the hyperuricemia induced by **furosemide**

AUTHOR(S): Schirmeister, J.; Man, N. K.; Hallauer, W.

CORPORATE SOURCE: Med. Universitaetsklin., Freiburg/Br., Fed. Rep. Ger.

SOURCE: Progr. Nephrol., Proc. Symp. "Ges. Nephrol.", 5th (1969), Meeting Date 1967, 59-63. Editor(s): Peters, Georges. Springer: Berlin, Ger.

CODEN: 23QNA2

DOCUMENT TYPE: Conference

LANGUAGE: English

AB Studies were carried out in order to define the renal and extrarenal factors by which **furosemide** modifies the serum uric acid (SUA) concn. The renal effect of **furosemide** in man appears to be 2-fold. First an initial small decrease of urinary urate excretion which could be due to an increased proximal tubular reabsorption of uric acid, enhanced by an increased blood lactate. It is suggested that the 2nd renal effect could be a **depression** of tubular secretion of urate which abolishes the increase in uric acid excretion, expected as a consequence of the augmented uric acid load.



L14 ANSWER 1 OF 106 USPATFULL on STN

ACCESSION NUMBER: 2002:332768 USPATFULL  
TITLE: Methods and compositions for treating conditions of the  
central and peripheral nervous systems using  
non-synaptic mechanisms  
INVENTOR(S): Hochman, Daryl W., Seattle, WA, United States  
PATENT ASSIGNEE(S): Cytoscan Sciences LLC, Seattle, WA, United States (U.S.  
corporation)

|                     | NUMBER         | KIND | DATE         |
|---------------------|----------------|------|--------------|
| PATENT INFORMATION: | US 6495601     | B1   | 20021217     |
| APPLICATION INFO.:  | US 1999-470637 |      | 19991222 (9) |

|                       | NUMBER                                  | DATE          |
|-----------------------|---|---------------|
| PRIORITY INFORMATION: | US 1998-113620P                         | 19981223 (60) |
| DOCUMENT TYPE:        | Utility                                 |               |
| FILE SEGMENT:         | GRANTED                                 |               |
| PRIMARY EXAMINER:     | Fay, Zohreh                             |               |
| ASSISTANT EXAMINER:   | Kwon, Brian Yong S                      |               |
| LEGAL REPRESENTATIVE: | Speakman, Ann W., Friedman, Susan J.    |               |
| NUMBER OF CLAIMS:     | 6                                       |               |
| EXEMPLARY CLAIM:      | 1                                       |               |
| NUMBER OF DRAWINGS:   | 35 Drawing Figure(s); 8 Drawing Page(s) |               |
| LINE COUNT:           | 2851                                    |               |

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to methods and compositions for treating selected conditions of the central and peripheral nervous systems employing non-synaptic mechanisms. More specifically, one aspect of the present invention relates to methods and materials for treating seizure and seizure disorders, epilepsy, status epilepticus, **migraine**, spreading **depression**, intracranial hypertension; for treating the pathophysiological effects of head trauma, stroke, ischemia and hypoxia; for treating or protecting from the pathophysiological effects of neurotoxic agents such as ethanol; and for treating neuropsychiatric disorders and central nervous system edema by administering agents that modulate ionic concentrations and/or ionic gradients in the brain, particularly ion-dependent or cation-chloride cotransporter antagonists. Ion-dependent cotransport antagonists and combinations of such compositions with other agents for treating various conditions are disclosed. The present invention also relates to methods and compositions for treating pain by administering ion-dependent cotransporter antagonists. Methods and compositions for enhancing cortical function, for example, in centers of cognition, learning and memory, by administering ion-dependent cotransporter agonists are disclosed. Methods and systems for screening drug candidate compounds for desired activities using in vitro and in vivo systems are disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 2 OF 106 CAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1975:508130 CAPLUS  
DOCUMENT NUMBER: 83:108130  
TITLE: Renal secretion of sulfur-35 labeled-  
**furosemide** and its **depression** by  
albumin binding  
AUTHOR(S): Bowman, R. H.  
CORPORATE SOURCE: VA Hosp., Syracuse, NY, USA  
SOURCE: American Journal of Physiology (1975), 229(1), 93-8  
CODEN: AJPHAP; ISSN: 0002-9513  
DOCUMENT TYPE: Journal  
LANGUAGE: English

GI For diagram(s), see printed CA Issue.  
AB It was detd. by use of 35S-labeled **furosemide** (I) [54-31-9] and an ultrafiltration procedure that **furosemide** is bound extensively to bovine serum albumin. When 500 .mu.moles **furosemide** and albumin at a concn. of 2.5 g/100 ml were used, approx. 90% of the drug was bound. With this same amt. of **furosemide**, but with 3 times as much albumin, binding was about 98%. Using a 25-fold lower concn. of **furosemide**, 20 .mu.moles, binding was nearly 98% with 2.5 g albumin/100 ml, and was over 98% with 7.5 g albumin/100 ml. These same concns. of **furosemide** and albumin were used to investigate the excretory and secretory rates of 35S-labeled **furosemide** in the isolated perfused rat kidney. Tubular clearance (i.e., secretion) of **furosemide** was inversely related to the concn. of albumin in the perfusate. In kidneys perfused without albumin, tubular clearance of the drug was 6-20 times that found when 2.5 or 7.5 g albumin/100 ml, resp., was used. Probenecid, with or without albumin, reduced the clearance of **furosemide** to that of its filtration rate. Thus, at physiol. albumin concns., a very small fraction of circulating **furosemide** will be available for filtration, and tubular-fluid and urinary **furosemide** will arise predominantly from secretion. Because of extensive binding of **furosemide** to albumin, the renal secretory process itself would be depressed, and the rate of secretion will be dependent, in part, on the concn. of unbound drug.

L14 ANSWER 3 OF 106 CAPLUS COPYRIGHT 2003 ACS on STN  
ACCESSION NUMBER: 1982:97452 CAPLUS  
DOCUMENT NUMBER: 96:97452  
TITLE: Comparative acute cochlear toxicity of intravenous bumetanide and **furosemide** in the purebred beagle  
AUTHOR(S): Brown, R. Don  
CORPORATE SOURCE: Sch. Med., Louisiana State Univ., Shreveport, LA, 71130, USA  
SOURCE: Journal of Clinical Pharmacology (1981), 21(11-12, Pt. 2), 620-7  
CODEN: JPCPBR; ISSN: 0091-2700  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
AB Comparisons were made of the effects of various doses of i.v. bumetanide [28395-03-1] and **furosemide** [54-31-9] on the primary auditory afferent activity (N1) and cochlear microphonics (CM) of beagles. The dose-response relations of the N1 **depressions** to bumetanide and **furosemide** are parallel; those of the CM **depressions** are also parallel but have a much shallower slope than those of the N1 **depressions**. With both drugs, N1 **depression** occurs at lower doses than does CM **depression**. The N1 **depression** produced by a particular dose of bumetanide or **furosemide** bore a linear relation to the CM **depression** produced. This finding supports the postulate that the cochlear site and mechanism of ototoxic action of the loop **diuretics** are directed at an earlier step of the cochlear transduction process than N1. Using N1 **depression** as the gross electrophysiol. index of ototoxicity, the acute ototoxic potency of bumetanide in beagles is .apprx.6.5 times that of **furosemide**, whereas its diuretic potency is 40-60 times that of **furosemide**. Therefore, when clin. dosages of the 2 drugs are considered, the relative acute ototoxic potency of bumetanide in the beagle is 0.11-0.16 that of **furosemide**. This range is identical to the relative ototoxic potency of 0.11-0.16 previously obtained in the cat. Serum concns. of bumetanide and **furosemide** increased linearly with the doses of the 2 drugs, except for the highest dose given (100 mg/kg for both drugs). The serum concns. at that dose of both drugs are less than the math. predicted values. Histol. (light-microscopic) examn. of the cochleas did not reveal any significant pathol.

L14 ANSWER 4 OF 106 CAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1969:53966 CAPLUS  
DOCUMENT NUMBER: 70:53966  
TITLE: Effects of **diuretics** on respiration and changes in tissue sodium and potassium concentrations  
AUTHOR(S): Herms, Wolfgang; Kersting, Friedhelm  
CORPORATE SOURCE: I Med. Klin., Univ. Duesseldorf, Duesseldorf, Fed. Rep. Ger.  
SOURCE: Zeitschrift fuer die Gesamte Experimentelle Medizin (1969), 149(1), 13-24  
CODEN: ZGEMAZ; ISSN: 0372-8722  
DOCUMENT TYPE: Journal  
LANGUAGE: German

AB O consumption and restoration of K<sup>+</sup> by K<sup>+</sup>-depleted rabbit kidney cortical slices were studied in incubation media contg. p-chloromercuribenzoate (4 .times. 10<sup>-4</sup> moles/l.), N-ethylmaleimide (10<sup>-4</sup> moles/l.), and the diuretic agents, mersalyl (200-800 mg./l.), **hydrochlorothiazide** (100-400 mg./l.), **furosemide** (40-320 mg./l.), and ethacrynic acid (40-320 mg./l.). With increasing doses of all compds. tested, a decrease in O consumption, a decrease in K<sup>+</sup> restoration, and an increase in tissue Na<sup>+</sup> concn. were observed as compared with controls. No correlation between the **depression** rate of respiration and the decrease in K<sup>+</sup> uptake was observed, except with **hydrochlorothiazide**. With **furosemide** and ethacrynic acid, the decrease in O consumption was proportionately higher than the decrease in K<sup>+</sup> restoration, whereas with mersalyl, the inhibition of K<sup>+</sup> uptake paralleled the inhibition of respiration. No relation between the changes in K<sup>+</sup> concns. and reciprocal Na<sup>+</sup> concns. was observed. The increase in tissue Na<sup>+</sup> was relatively higher than the decrease in K<sup>+</sup> restoration, as compared with controls, esp. with ethacrynic acid, suggesting an addnl. effect on a K<sup>+</sup> and O insensitive Na<sup>+</sup> pump. Cysteine chloride, added at twice the molar concn., reversed the effect of N-ethylmaleimide on tissue respiration and on the Na<sup>+</sup> and K<sup>+</sup> ion concns., but had only minor effects on p-chloromercuribenzoate, **hydrochlorothiazide**, and mersalyl, and almost no effect on **furosemide** induced changes.

L14 ANSWER 5 OF 106 CAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1990:191432 CAPLUS  
DOCUMENT NUMBER: 112:191432  
TITLE: The influence of **furosemide** on plasma elimination and urinary excretion of drugs in standardbred horses  
AUTHOR(S): Stevenson, A. J.; Weber, M. P.; Todi, F.; Mendonca, M.; Fenwick, J. D.; Kwong, E.; Young, L.; Leavitt, R.; Nespolo, R.; et al.  
CORPORATE SOURCE: Race Track Div., Agric. Canada, Ottawa, ON, K2C 3X7, Can.  
SOURCE: Journal of Veterinary Pharmacology and Therapeutics (1990), 13(1), 93-104  
CODEN: JVPTD9; ISSN: 0140-7783  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB The effects of i.v. administration of 150 or 250 mg of **furosemide** to standardbred mares pre-treated with 9 other drugs were studied. **Furosemide** reduced the plasma concns. of codeine compared to control 2-6 h after **furosemide** administration. The plasma concns. of theophylline, phenylbutazone, pentazocine, guaifenesin, and flunixin were not markedly altered by **furosemide**. In the case of acepromazine, clenbuterol, and fentanyl, the data generated were insufficient. A significant redn. was noted in the urinary concns. of guaifenesin, acepromazine, clenbuterol, phenylbutazone, flunixin, fentanyl, and pentazocine within 1-4 h of **furosemide** administration. The urinary concns. of theophylline remained reduced as

long as 8 h after **furosemide** injection. **Furosemide** administration to horses pre-treated with codeine resulted in **depression** of urinary morphine concns. 2-4 h and 9-12 h after **furosemide** injection. A lower **furosemide** dose produced changes in drug urinary excretion and plasma elimination equiv. to the higher dose. Thus, **furosemide** affects the urinary and plasma concns. of other co-administered drugs but not in a predictable fashion, which limits the extrapolation of these results to as yet untested drugs.

L14 ANSWER 6 OF 106 USPATFULL on STN

ACCESSION NUMBER: 2003:11156 USPATFULL  
TITLE: Treatment of congestive heart failure  
INVENTOR(S): Bakker-Arkema, Rebecca Guggemos, Ann Arbor, MI, UNITED STATES  
Pressler, Milton Lethan, Saline, MI, UNITED STATES

|                       | NUMBER   | KIND | DATE          |
|-----------------------|--|------|---------------|
| PATENT INFORMATION:   | US 2003008860  | A1   | 20030109      |
| APPLICATION INFO.:    | US 2002-129892   | A1   | 20020509 (10) |
|                       | WO 2001-US9265   |      | 20010322      |
| DOCUMENT TYPE:        | Utility  |      |               |
| FILE SEGMENT:         | APPLICATION  |      |               |
| LEGAL REPRESENTATIVE: | Charles W Ashbrook, Warner Lambert Company, 2800 Plymouth Road, Ann Arbor, MI, 48105 |      |               |
| NUMBER OF CLAIMS:     | 15   |      |               |
| EXEMPLARY CLAIM:      | 1  |      |               |
| NUMBER OF DRAWINGS:   | 4 Drawing Page(s)  |      |               |
| LINE COUNT:           | 856  |      |               |

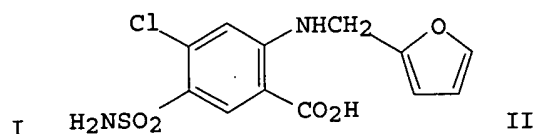
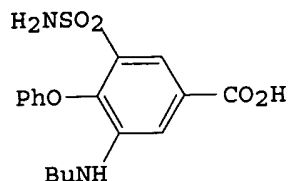
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Combinations of **diuretics** and vasopressin antagonists are useful to slow and reverse the symptoms and process of congestive heart failure, to increase the excretion of water in the urine, and to decrease the excretion of sodium and potassium ions in urine. Preferred vasopressin antagonists have the formula (I) wherein R and R.sup.5 are hydrogen or lower alkyl; R.sup.1, R.sup.2, and R.sup.3 are hydrogen, halo, alkyl, alkoxy, and amino; and R.sup.4 is hydrogen or phenyl, and a pharmaceutically acceptable salt thereof

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L14 ANSWER 7 OF 106 CAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1979:449579 CAPLUS  
DOCUMENT NUMBER: 91:49579  
TITLE: Comparative acute ototoxicity of intravenous bumetanide and **furosemide** in the pure-bred beagle  
AUTHOR(S): Brown, R. Don; Manno, Joseph E.; Daigneault, Ernest A.; Manno, Barbara R.  
CORPORATE SOURCE: Sch. Med. Shreveport, Louisiana State Univ., Shreveport, LA, 71130, USA  
SOURCE: Toxicology and Applied Pharmacology (1979), 48(1, Pt. 1), 157-69  
CODEN: TXAPA9; ISSN: 0041-008X  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
GI



AB The effects of various doses of i.v. bumetanide (I) [28395-03-1] and furosemide (II) [54-31-9] on the auditory afferent activity (N1) and cochlear microphonics (CM) of beagles were detd. in a quant. manner. Serum concns. of these 2 loop diuretics were also detd. at 3.5 min after the injections in the majority of the animals. The dose-response relationships of the N1 depressions to I and II were parallel; those of the CM depressions were also parallel but had a much shallower slope than those of the N1 depressions. With both drugs, N1 depression occurred at lower doses than did CM depression. When multiple linear regression anal. was performed, the N1 depression produced by a particular dose of I or II bore a linear relationship to the CM depression produced. Thus, the cochlear site and mechanism of ototoxic action of the loop diuretics were directed at an earlier step of the cochlear transduction process than N1. Serum concns. of I and II increased linearly with the doses of the 2 drugs, except for the highest dose given (100 mg/kg for both drugs). The serum concns. at the dose of both drugs were lower than the math. predicted values. Histol. examn. of the cochleas did not reveal any significant pathol. changes produced in the stria vascularis, outer and inner hair cells, afferent and efferent nerve terminals, or the spiral ganglia and efferent nerve bundles. Using N1 depression as the gross electrophysiologic index of ototoxicity, the acute ototoxic potency of I in beagles was .apprx.6.5 times that of II, whereas its diuretic potency was 40-60 times that of II. Therefore, when clin. dosages of the 2 drugs were considered, the relative, acute ototoxic potency of I in the beagle was 0.11-0.16 that of II. This range was identical to the relative ototoxic potency of 0.11-0.16 previously obtained in the cat.

L14 ANSWER 8 OF 106 CAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1973:474270 CAPLUS

DOCUMENT NUMBER: 79:74270

TITLE: Diuretic depression of fluorescein secretion in the proximal tubules of frog kidney. Vital examination by contact microscopy

AUTHOR(S): Bresler, V. M.; Natochin, Yu. V.

CORPORATE SOURCE: I. M. Sechanov Inst. Evol. Physiol. Biochem., Leningrad, USSR

SOURCE: Byulleten Eksperimental'noi Biologii i Meditsiny (1973), 75(6), 67-9  
CODEN: BEBMAE; ISSN: 0365-9615

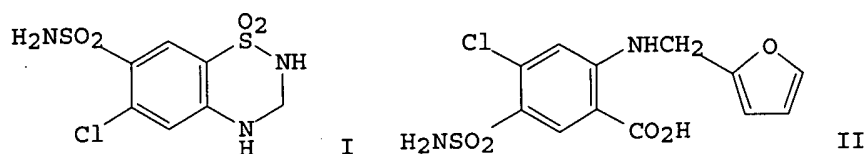
DOCUMENT TYPE: Journal

LANGUAGE: Russian

AB Frog kidney proximal tubule cells intensely secreted fluorescein [2321-07-5] after administration of the compd. in vivo or to an isolated kidney. The diuretics furosemide (I) [54-31-9], ethacrynic acid [58-54-8], triampur (triamterene) [396-01-0], brinaldix [636-54-4], and an aldactone-saltucin mixt. [39394-35-9], administered in doses which prevented Na resorption, inhibited the passage of fluorescein through the apical membrane and the lumen of the proximal tubules, but did not affect fluorescein accumulation in the cells of the tubules. Apparently the depression of fluorescein secretion by the diuretics was due to the effects of the compds. on the system of Na transport located in the apical plasmatic membrane of the proximal

tubules.

L14 ANSWER 9 OF 106 CAPLUS COPYRIGHT 2003 ACS on STN  
ACCESSION NUMBER: 1981:202614 CAPLUS  
DOCUMENT NUMBER: 94:202614  
TITLE: The role of intrarenal prostaglandin E in the action  
of **diuretics**  
AUTHOR(S): Dagher, Georges; Berbari, Adel  
CORPORATE SOURCE: Hop. Necker, Paris, 75015, Fr.  
SOURCE: Developments in Endocrinology (Amsterdam) (1980),  
10 (Horm. Regul. Sodium Excretion), 213-20  
CODEN: DENDD4; ISSN: 0165-1900  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
GI



AB In rats, **hydrochlorothiazide** (I) [58-93-5] and **furosemide** (II) [54-31-9] induced a diuresis and natriuresis of similar magnitude with no change in plasma or renal PGE levels. The diuretic response following I in indomethacin-treated rats was less marked, and was assocd. with a redn. in plasma and renal PGE levels. Na or K excretions were unchanged. The potentiation of II-induced diuresis and natriuresis by indomethacin was assocd. with a **depression** in renal prostaglandins. Indomethacin treatment inhibited hyperreninemia of II-treated rats. Apparently, intrarenal PGE plays a role in the mechanism of II diuresis and natriuresis in the rat.

L14 ANSWER 10 OF 106 CAPLUS COPYRIGHT 2003 ACS on STN  
ACCESSION NUMBER: 1970:475301 CAPLUS  
DOCUMENT NUMBER: 73:75301  
TITLE: Ototoxicity of new and potent **diuretics**  
AUTHOR(S): Mathog, Robert H.; Thomas, William G.; Hudson, William R.  
CORPORATE SOURCE: Med. Center, Duke Univ., Durham, NC, USA  
SOURCE: Archives of Otolaryngology (1970), 92(1), 7-13  
CODEN: AROTA; ISSN: 0003-9977  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB Ethacrynic acid and **furosemide** produced a primary **depression** of the cochlear microphonic and action potential in cats; complete recovery ensued within 1 hr. A secondary **depression** with outer hair cell degeneration in the basal and middle coils of the cochlea was obsd. after high doses of ethacrynic acid.

L14 ANSWER 11 OF 106 CAPLUS COPYRIGHT 2003 ACS on STN  
ACCESSION NUMBER: 1967:54072 CAPLUS  
DOCUMENT NUMBER: 66:54072  
TITLE: Action of **diuretics** in dogs studied by micropuncture  
AUTHOR(S): Berliner, Robert W.; Dirks, John H.; Cirkse, William J.  
CORPORATE SOURCE: Natl. Health Inst., Bethesda, MD, USA  
SOURCE: Annals of the New York Academy of Sciences (1966), 139(2), 424-32

CODEN: ANYAA9; ISSN: 0077-8923

DOCUMENT TYPE: Journal  
LANGUAGE: English

AB Depressed reabsorption in the accessible portion of the proximal tubule of the dog kidney contributed to the diuresis which followed the administration of **hydrochlorothiazide** (2 mg./kg.), **furosemide** (5 and 25 mg./kg.), chlormerodrin (2 mg./kg.), and ethacrynic acid (1 and 5 mg./kg.). The effects of infusing isotonic saline soln., detected as a **depression** of reabsorption in the proximal convoluted tubule, were assocd. with greater reabsorption of Na salts and H<sub>2</sub>O in the loop of Henle and beyond, than previously thought. These amts. were large enough to explain the magnitude of the diuresis involved.

L14 ANSWER 12 OF 106 CAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1970:65055 CAPLUS

DOCUMENT NUMBER: 72:65055

TITLE: Effect of **furosemide** on sodium and potassium ion transport studied by microperfusion of the rat nephron

AUTHOR(S): Morgan, Trefor; Tadokoro, Masao; Martin, Denis G.; Berliner, Robert W.

CORPORATE SOURCE: Nat. Heart Inst., Nat. Inst. of Health, Bethesda, MD, USA

SOURCE: American Journal of Physiology (1970), 218(1), 292-7  
CODEN: AJPHAP; ISSN: 0002-9513

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Proximal tubules, loops of Henle, and distal tubules were perfused with a soln. contg. **furosemide** (1-10 mg/l.) and the net transport of Na<sup>+</sup> and K<sup>+</sup> was compared with that obtained during control perfusions. In addn., the ability of the proximal tubule to create a gradient for Na<sup>+</sup> when raffinose was in the perfusate was detd. in the presence and absence of **furosemide**. Net Na absorption in the proximal tubule as measured by water absorption decreased from 1.31  $\pm$  0.07 to 0.77  $\pm$  0.14 nl./min/mm. The concn. difference developed in the presence of raffinose fell from 2.43  $\pm$  0.8 to 15.3  $\pm$  0.9 mequiv./l. when **furosemide** was present. Net absorption by the loop of Henle decreased from 1.79 to 0.85 nequiv./m in for Na and from 0.034 to -0.009 nequiv./min for K. No **depression** of Na transport was detected in the distal tubule. Although K entered the perfusate in the distal tubule, it was difficult to det. whether the rate of entry was affected by **furosemide**. The changes obsd. appear to account for the pattern of Na and K excretion of urine.

L14 ANSWER 13 OF 106 CAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1980:631010 CAPLUS

DOCUMENT NUMBER: 93:231010

TITLE: Interaction of conventional and antikaliuretic **diuretics** with the renal prostaglandin system

AUTHOR(S): Kramer, H. J.; Duesing, R.; Stinnesbeck, B.; Prior, W.; Baecker, Angela; Eden, Jutta; Kipnowski, J.; Glaenger, K.; Krueck, F.

CORPORATE SOURCE: Poliklin., Med. Univ., Bonn, Fed. Rep. Ger.

SOURCE: Clinical Science (1980), 59(1), 67-70

CODEN: CSCIAE; ISSN: 0143-5221

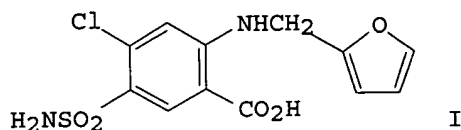
DOCUMENT TYPE: Journal

LANGUAGE: English

AB Urinary excretion of PGE<sub>2</sub> [363-24-6] was increased from 1.24 to 2.60, 2.93, and 4.28 mmol/24 h by frusemide [54-31-9], **hydrochlorothiazide** (I) [58-93-5], and spironolactone [52-01-7], resp. A rise in PGF<sub>2</sub>.alpha. [551-11-1] induced by I was quant. similar but statistically insignificant. I- and frusemide-induced Na excretion was reduced by indomethacin [53-86-1] as was spironolactone-induced K

sparing and the rise in plasma renin [9015-94-5] obsd. with all 3 **diuretics**. Indomethacin enhanced urinary osmolality and free water absorption in the presence of spironolactone but not I or frusemide. Thus, increased prostaglandin activity after **diuretics** may contribute to their natriuretic action; this and the antikaliuretic effect of spironolactone may be partially abolished by nonsteroidal antiphlogistic agents.

L14 ANSWER 14 OF 106 CAPLUS COPYRIGHT 2003 ACS on STN  
 ACCESSION NUMBER: 1978:15724 CAPLUS  
 DOCUMENT NUMBER: 88:15724  
 TITLE: Effects of **furosemide** on glomerular filtration rate and clearance of practolol, digoxin, cephaloridine, and gentamicin  
 AUTHOR(S): Tilstone, W. J.; Semple, P. F.; Lawson, D. H.; Boyle, J. A.  
 CORPORATE SOURCE: Dep. Pharm. Chem., Univ. Strathclyde, Glasgow, UK  
 SOURCE: Clinical Pharmacology & Therapeutics (St. Louis, MO, United States) (1977), 22(4), 389-94  
 CODEN: CLPTAT; ISSN: 0009-9236  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 GI



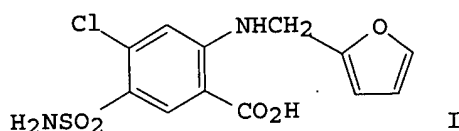
AB **Furosemide** (I) [54-31-9] decreased inulin clearance in 20 of 27 normal subjects. The **depression** in inulin clearance occurred in both water-loaded and non-water-loaded subjects. The renal clearance of practolol [6673-35-4], but not digoxin [20830-75-5], was reduced when I was given. The av. total plasma clearances of gentamicin [1403-66-3] and cephaloridine [50-59-9] over a 6-h period were decreased after I. The reduced clearances of the antibiotics were assocd. with higher plasma levels, the increase in antibiotic concn. being as much as 100% at 1 h after an i.v. bolus injection.

L14 ANSWER 15 OF 106 CAPLUS COPYRIGHT 2003 ACS on STN  
 ACCESSION NUMBER: 1987:207410 CAPLUS  
 DOCUMENT NUMBER: 106:207410  
 TITLE: Effects of dipyrindamole and **furosemide** on renal function during adenine infusion in rats  
 AUTHOR(S): Redlak, Maria; Szczepanska-Konkel, Mirosława; Stepinski, Jan; Angielski, Stefan  
 CORPORATE SOURCE: Zakł. Biochem. Klin., Akad. Med., Gdansk, 80-227, Pol.  
 SOURCE: Acta Physiologica Polonica (1986), 37(1), 1-7  
 CODEN: APYPAY; ISSN: 0044-6033  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB I.v. infusion of NAD [53-84-9] (200 nmole/kg/min) to rats decreased urine flow, renal plasma flow, glomerular filtration rate, and urinary excretion of Na<sup>+</sup> and adenosine (I) [58-61-7] but increased plasma I concn. Infusion of NAD (50 nmole/kg/min) or dipyrindamole [58-32-2] (25 .mu.g/h/min) affected neither renal function nor plasma I levels but infusion of the agents together depressed renal function and raised plasma I. **Furosemide** [54-31-9] failed to abolish the renal function **depression** induced by NAD.

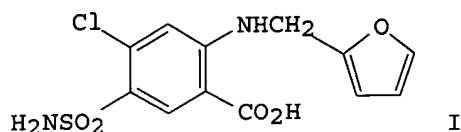


L14 ANSWER 16 OF 106 CAPLUS COPYRIGHT 2003 ACS on STN  
 ACCESSION NUMBER: 1981:96176 CAPLUS  
 DOCUMENT NUMBER: 94:96176  
 TITLE: Pharmacologic determinants of ototoxicity of **furosemide** in the chinchilla  
 AUTHOR(S): Green, Thomas P.; Rybak, Leonard P.; Mirkin, Bernard L.; Juhn, S. K.; Morizono, Tetsuo  
 CORPORATE SOURCE: Dep. Pharmacol., Univ. Minnesota, Minneapolis, MN, 55455, USA  
 SOURCE: Journal of Pharmacology and Experimental Therapeutics (1981), 216(3), 537-42  
 CODEN: JPETAB; ISSN: 0022-3565  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 GI



AB In chinchillas 15 min after the administration of an ototoxic dose of **furosemide** (I) [54-31-9] (100 mg/kg, i.v.) the highest concn. of I was found in perilymph. Elimination of the drug from perilymph paralleled that from serum, and a 65:1 drug concn. gradient (serum/perilymph) was rapidly established and maintained. The same gradient was found after other ototoxic I doses (25-200 mg/kg) and after chronic I administration. The magnitude of this gradient could not be accounted for by binding of I to serum proteins, by pH-dependent drug partitioning or by cochlear drug glucuronidation. The drug elimination profile from perilymph was most consistent with free penetration of drug into the inner ear coupled with rapid removal. The time course of endocochlear potential **depression** was strikingly similar to the I-perilymph concn. time curve; maximal endocochlear potential **depression** occurred at 5 to 15 min following the i.v. dose, corresponding with the time of peak perilymph I levels, but not with local diuretic effects on electrolytes. Calcns. based on the pharmacokinetic data revealed that I produced **depression** of endocochlear potential only at doses sufficient to produce I perilymph concns. >1.3 .mu.g/mL. Furthermore, this potential remained depressed only as long as the local I concn. exceeded this same threshold value. Apparently, the ototoxicity of I is related directly to drug penetration rather than mediated through secondary effects on electrolytes.

L14 ANSWER 17 OF 106 CAPLUS COPYRIGHT 2003 ACS on STN  
 ACCESSION NUMBER: 1983:11226 CAPLUS  
 DOCUMENT NUMBER: 98:11226  
 TITLE: Effects of **furosemide** on the neuromuscular junction  
 AUTHOR(S): Scappaticci, K. A.; Ham, J. A.; Sohn, Y. J.; Miller, R. D.; Dretchen, K. L.  
 CORPORATE SOURCE: Sch. Med. Dent., Georgetown Univ., Washington, DC, 20007, USA  
 SOURCE: Anesthesiology (1982), 57(5), 381-8  
 CODEN: ANESAV; ISSN: 0003-3022  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 GI



AB The effects of **furosemide** (I) [54-31-9] on neuromuscular transmission were studied using the in vitro rat phrenic nerve diaphragm and the in vivo cat soleus nerve muscle prepns. I (10<sup>-6</sup>-10<sup>-4</sup> M) reduced the concn. of d-tubocurarine required to achieve 50% twitch tension **depression** in the indirectly stimulated rat diaphragm. Intraarterial injection of I had a biphasic effect on the cat neuromuscular junction. At low doses (0.1-10.0  $\mu$ g/kg) the drug had a depressant effect, reduced the force of muscle contraction, prevented nerve and muscle responses to NaF and dibutyryl cyclic AMP, and intensified the neuromuscular blockade produced by d-tubocurarine and succinylcholine. In contrast, in higher doses (1-4 mg/kg) I produced stimulus-bound repetitive neural activity, initiated neural activity, increased the force of muscle contraction, enhanced nerve and muscle responses to NaF and dibutyryl cyclic AMP, and antagonized d-tubocurarine and succinylcholine blockades. I had no effect on denervated prepns. High doses of I inhibit noncompetitively both the high- and low-affinity forms of the enzyme cyclic AMP phosphodiesterase in both sol. and particulate fractions of cat sciatic nerve. Thus, I has direct effects on neuromuscular transmission, but the direction of these effects is dose-dependent.

L14 ANSWER 18 OF 106 CAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1988:522273 CAPLUS

DOCUMENT NUMBER: 109:122273

TITLE: Lithium clearance as an indicator of proximal tubular sodium handling during **furosemide** diuresis

AUTHOR(S): Christensen, Sten; Shalmi, Michael; Petersen, Joergen S.

CORPORATE SOURCE: Dep. Pharmacol., Univ. Copenhagen, Copenhagen, DK-2100, Den.

SOURCE: Journal of Pharmacology and Experimental Therapeutics (1988), 246(2), 753-7  
CODEN: JPETAB; ISSN: 0022-3565

DOCUMENT TYPE: Journal

LANGUAGE: English

AB To evaluate the use of the renal Li clearance as an indicator of proximal tubular Na handling during **furosemide** diuresis, clearance expts. were performed in conscious catheterized rats. Maximal **depression** of proximal Na reabsorption was induced by isotonic saline expansion (40 mL/h) and under these conditions **furosemide** (7.5 mg/kg/h) did not increase abs. or fractional clearance of Li. These results provide indirect evidence against the existence of a **furosemide** -sensitive Li reabsorption in the ascending limb of Henle. The increase of abs. and fractional Li clearance obsd. in nonexpanded animals given **furosemide** therefore most likely reflects inhibition of electrolyte reabsorption in the proximal tubules. Using Li clearance as a measure for Na output from the proximal tubules, the study provided information about the contribution of proximal and distal nephron segments to saline expansion natriuresis. Apparently, the natriuresis is caused by enhanced delivery of Na from the proximal tubules, which is only partially compensated for by a load-dependent increase of abs. distal Na reabsorption, most likely occurring in the thick ascending limb of Henle.

L14 ANSWER 19 OF 106 CAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1975:422347 CAPLUS

DOCUMENT NUMBER: 83:22347

TITLE: Comparison of the cochlear toxicity of sodium ethacrylate, **furosemide**, and the cysteine adduct of sodium ethacrylate in cats

AUTHOR(S): Brown, R. Don

CORPORATE SOURCE: Sch. Med., Louisiana State Univ., Shreveport, LA, USA

SOURCE: Toxicology and Applied Pharmacology (1975), 31(2), 270-82  
CODEN: TXAPA9; ISSN: 0041-008X

DOCUMENT TYPE: Journal

LANGUAGE: English

GI For diagram(s), see printed CA Issue.

AB The durations of the N1 **depression** in anesthetized cats produced by i.v. administration of Na ethacrylate (I) [6500-81-8] (5.0 mg/kg) and the cysteine adduct of Na ethacrylate (II) [51246-37-8] (2.4 mg/kg) were much longer than that produced by **Furosemide** (III) [54-31-9] (12.0 mg/kg). However, the dose-response curves for I, II and III were parallel with II having the greatest potency followed by I and then III. The dose-time to max. effect curves were also parallel with II being the fastest followed by III and then I, which had an irreducible latent period. Thus, all 3 agents appear to produce ototoxicity by acting on the same cochlear site by the same mechanism of action. The difference in duration of N1 **depression** were probably due to I and II not diffusing out of the cochlea as readily as III, or to III being inactivated by cochlear tissue. Also, I may be converted partly or wholly to II before exerting an ototoxic effect.

L14 ANSWER 20 OF 106 CAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1977:593958 CAPLUS

DOCUMENT NUMBER: 87:193958

TITLE: Effects of some **diuretics** and metabolic inhibitors on the sodium transport and electrical properties of the intestinal mucous membrane of the rat in situ

AUTHOR(S): Shida, Masaru; Kikuchi, Shintaro

CORPORATE SOURCE: Cent. Res. Div., Takeda Chem. Ind. Ltd., Osaka, Japan

SOURCE: Takeda Kenkyushoho (1977), 36(1-2), 53-63  
CODEN: TAKHAA; ISSN: 0371-5167

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The rat small intestine at the transitional part between the jejunum and ileum was suspended in situ in physiol. saline at 32 to 34.degree. and the transepithelial p.d. (PD), short circuit current (SCC) and sp. resistance (Re) were recorded to give the values 3 to 11 mV, 37 to 142 .mu.A/cm2 and 38 to 204 .OMEGA.cm2, resp. Addn. of 3 .times. 10-3 M NaCN to the intraluminal fluid, composed of 10 mM glucose and 145 mM NaCl, depressed the Na influx across the mucous membrane by 47%, assocd. with **depression** of the transepithelial PD and SCC equally by about 60%. A similar **depression** of the Na influx caused by addn. of 10-3 M 2,4-dinitrophenol [51-28-5] or 10-3 M iodoacetic acid [64-69-7] was accompanied by **depression** of the PD and ACC by about 20%. The transepithelial Re was not changed by the addn. of these metabolic inhibitors. The intraluminal administration of **diuretics** also depressed concn.-dependently the Na influx. The relatively similar **depression** of the Na influx by 35 to 45% caused by **hydrochlorothiazide** [58-93-5], amiloride [2609-46-3], or 10-3 M DS-511 [1,4-dimorpholino-7-phenylpyrido[3,4-d]pyridazine] [39632-88-7] was accompanied by the decrease of the SCC by 13, 11 and 24% but by the increase of the transepithelial PD was not significantly affected by any of these **diuretics**. **Furosemide** [54-31-9] (6 .times. 10-4 M) depressed the Na influx, PD, SCC and Re by 39, 32, 19 and 15%, resp. Acetazolamide [59-66-5] (10-3 M) depressed only the Na influx and SCC by 23 and 6%, resp. None of the metabolic inhibitors or the **diuretics**, when applied serosally in physiol. saline at the corresponding concn., nor the **diuretics** injected i.v. affected

the Na influx or the elec. properties of the mucous membrane.

(FILE 'HOME' ENTERED AT 16:06:01 ON 03 OCT 2003)

FILE 'CAPLUS, MEDLINE, BIOSIS, EMBASE' ENTERED AT 16:06:14 ON 03 OCT 2003

L1 58209 S 54-31-9/RN OR FUROSEMIDE  
L2 23161 S ACETAZOLAMIDE OR DIAMOX  
L3 141415 S MIGRAINE OR HEADACHE  
L4 486 S L1 AND L3  
L5 622 S L2 AND L3  
L6 445 DUP REM L4 (41 DUPLICATES REMOVED)  
L7 449 DUP REM L5 (173 DUPLICATES REMOVED)  
L8 52 S L6 AND MIGRAINE  
L9 52 FOCUS L8 1-

=>

L9 ANSWER 15 OF 52 MEDLINE on STN

ACCESSION NUMBER: 1998114015 MEDLINE  
DOCUMENT NUMBER: 98114015 PubMed ID: 9453270  
TITLE: **Furosemide** inhibits regenerative cortical spreading depression in anaesthetized cats.  
AUTHOR: Read S J; Smith M I; Benham C D; Hunter A J; Parsons A A  
CORPORATE SOURCE: Neurosciences Research, SmithKline Beecham Pharmaceuticals, Harlow, Essex, UK.  
SOURCE: CEPHALALGIA, (1997 Dec) 17 (8) 826-32.  
Journal code: 8200710. ISSN: 0333-1024.  
PUB. COUNTRY: Norway  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199803  
ENTRY DATE: Entered STN: 19980319  
Last Updated on STN: 19980319  
Entered Medline: 19980310

AB Ionic perturbations occur during cortical spreading depression (SD), a phenomenon implicated in **migraine** pathophysiology. We studied the effect of 0.2, 2 and 20 mg kg<sup>-1</sup> i.v. (n=4) **furosemide** on cortical direct current (d.c.) potential, cerebrovascular laser Doppler flux (rCBF[LDF]), artery diameter and NO concentration in the parietal cortex of the anaesthetized cat during repetitive SD. In vehicle-treated animals (n=4), SD activity was sustained for 50+/-1.8 min. However, duration of SD activity was significantly reduced when compared to vehicle to 39+/-6.6 (n=4), 34+/-8.5 (n=4) and 27.3+/-11.3 min (n=4), at 0.2, 2 and 20 mg kg<sup>-1</sup> i.v. **furosemide** respectively. It is hypothesized that the mechanism of inhibition of SD d.c. activity by **furosemide** may be through alterations in cortical ion buffering capacity or inhibition of cell swelling in neurones or glia. These mechanisms may represent potential novel drug targets in future **migraine** therapy.

L9 ANSWER 32 OF 52 MEDLINE on STN  
ACCESSION NUMBER: 2000497652 MEDLINE  
DOCUMENT NUMBER: 20438668 PubMed ID: 10980751  
TITLE: Treatment of a prolonged migrainous aura with intravenous  
furosemide.  
AUTHOR: Rozen T D  
CORPORATE SOURCE: Jefferson Headache Center/Thomas Jefferson University  
Hospital, Philadelphia, PA 19107, USA..  
tood.rozen@mail.tju.edu  
SOURCE: NEUROLOGY, (2000 Sep 12) 55 (5) 732-3.  
Journal code: 0401060. ISSN: 0028-3878.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals  
ENTRY MONTH: 200010  
ENTRY DATE: Entered STN: 20001027  
Last Updated on STN: 20001027  
Entered Medline: 20001016

10 ANSWER 20 OF 20 REGISTRY COPYRIGHT 2003 ACS on STN

RN 54-31-9 REGISTRY

CN Benzoic acid, 5-(aminosulfonyl)-4-chloro-2-[(2-furanylmethyl)amino]- (9CI)  
(CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Anthranilic acid, 4-chloro-N-furfuryl-5-sulfamoyl- (8CI)

OTHER NAMES:

CN 2-Furfurylamino-4-chloro-5-sulfamoylbenzoic acid

CN 4-Chloro-N-(2-furylemethyl)-5-sulfamoylanthranilic acid

CN 4-Chloro-N-furfuryl-5-sulfamoylanthranilic acid

CN 5-(Aminosulfamyl)-4-chloro-2-[(2-furanylmethyl)amino]benzoic acid

CN Aisemide

CN Aldic

CN Aluzine

CN Anfuramaide

CN Apo-Frusemide

CN **Apo-Furosemide**

CN Aquamide

CN Aquarid

CN Aquasin

CN Arasemide

CN Beronald

CN Bioretic

CN Cetasix

CN Desdemin

CN Dirine

CN Disal

CN Discoid

CN Disemide

CN Diural

CN Diuresal

CN Diuretic salt

CN Diurin

CN Diurolasa

CN Diusemide

CN Diusil

CN Dranex

CN Dryptal

CN Durafurid

CN Edenol

CN Errolon

CN Eutensin

CN Fluidrol

CN Franyl

CN Frumex

CN Frumide

CN Frusedan

CN Frusema

CN Frusemide

CN Frusemin

CN Frusetic

CN Frusid

CN Fulsix

CN Fuluvamide

CN Furanthril

CN Furanthryl

CN **Furosemide**

ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for  
DISPLAY

FS 3D CONCORD

MF C12 H11 Cl N2 O5 S

CI COM

LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN\*, BIOBUSINESS, BIOSIS,  
BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN,

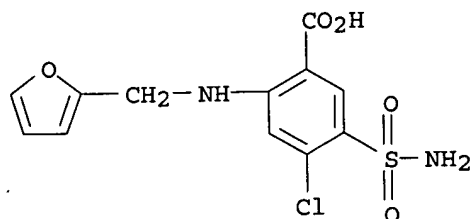


CHEMCATS, CHEMLIST, CIN, CSCHM, CSNB, DDFU, DIOGENES, DRUGU, EMBASE, GMELIN\*, HSDB\*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK\*, MSDS-OHS, NIOSHTIC, PHAR, PHARMASEARCH, PIRA, PROMT, RTECS\*, SPECINFO, TOXCENTER, ULIDAT, USAN, USPAT2, USPATFULL, VETU

(\*File contains numerically searchable property data)

Other Sources: DSL\*\*, EINECS\*\*, WHO

(\*\*Enter CHEMLIST File for up-to-date regulatory information)



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

4916 REFERENCES IN FILE CA (1907 TO DATE)

51 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

4927 REFERENCES IN FILE CAPLUS (1907 TO DATE)

66 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=>

L2 ANSWER 1 OF 1 USPATFULL on STN

ACCESSION NUMBER: 2002:332768 USPATFULL  
TITLE: Methods and compositions for treating conditions of the  
central and peripheral nervous systems using  
non-synaptic mechanisms  
INVENTOR(S): Hochman, Daryl W., Seattle, WA, United States  
PATENT ASSIGNEE(S): Cytoscan Sciences LLC, Seattle, WA, United States (U.S.  
corporation)

|                     | NUMBER         | KIND | DATE         |     |
|---------------------|----------------|------|--------------|-----|
| PATENT INFORMATION: | US 6495601     | B1   | 20021217     | <-- |
| APPLICATION INFO.:  | US 1999-470637 |      | 19991222 (9) |     |

|                       | NUMBER                                  | DATE          |
|-----------------------|---|---------------|
| PRIORITY INFORMATION: | US 1998-113620P                         | 19981223 (60) |
| DOCUMENT TYPE:        | Utility                                 |               |
| FILE SEGMENT:         | GRANTED                                 |               |
| PRIMARY EXAMINER:     | Fay, Zohreh                             |               |
| ASSISTANT EXAMINER:   | Kwon, Brian Yong S                      |               |
| LEGAL REPRESENTATIVE: | Speakman, Ann W., Friedman, Susan J.    |               |
| NUMBER OF CLAIMS:     | 6                                       |               |
| EXEMPLARY CLAIM:      | 1                                       |               |
| NUMBER OF DRAWINGS:   | 35 Drawing Figure(s); 8 Drawing Page(s) |               |
| LINE COUNT:           | 2851                                    |               |

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to methods and compositions for treating selected conditions of the central and peripheral nervous systems employing non-synaptic mechanisms. More specifically, one aspect of the present invention relates to methods and materials for treating seizure and seizure disorders, epilepsy, status epilepticus, migraine, spreading depression, intracranial hypertension; for treating the pathophysiological effects of head trauma, stroke, ischemia and hypoxia; for treating or protecting from the pathophysiological effects of neurotoxic agents such as ethanol; and for treating neuropsychiatric disorders and central nervous system edema by administering agents that modulate ionic concentrations and/or ionic gradients in the brain, particularly ion-dependent or cation-chloride cotransporter antagonists. Ion-dependent cotransport antagonists and combinations of such compositions with other agents for treating various conditions are disclosed. The present invention also relates to methods and compositions for treating pain by administering ion-dependent cotransporter antagonists. Methods and compositions for enhancing cortical function, for example, in centers of cognition, learning and memory, by administering ion-dependent cotransporter agonists are disclosed. Methods and systems for screening drug candidate compounds for desired activities using in vitro and in vivo systems are disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT Drug screening  
IT Epilepsy  
IT Hypoxia, animal  
IT Ischemia  
IT Mental disorder  
IT Seizures  
(Methods and ion-dependent cotransporter antagonist compds. for treating central and peripheral nervous system disorders and methods for screening the compds.)  
IT Biological transport  
(cation-chloride cotransporter antagonist; Methods and ion-dependent cotransporter antagonist compds. for treating central and peripheral nervous system disorders and methods for screening the compds.)

IT Nervous system  
(central, disease, including edema and cortical function disorder;  
Methods and ion-dependent cotransporter antagonist compds. for treating  
central and peripheral nervous system disorders and methods for  
screening the compds.)

IT Brain  
(cerebral cortex, spreading depression; Methods and ion-dependent  
cotransporter antagonist compds. for treating central and peripheral  
nervous system disorders and methods for screening the compds.)

IT Cognition

IT Learning

IT Memory, biological  
(disorder treatment; Methods and compds. for treating central and  
peripheral nervous system disorders and methods for screening the  
compds.)

IT Animal

IT Animal tissue culture

IT Organ, animal  
(for drug screening; Methods and ion-dependent cotransporter antagonist  
compds. for treating central and peripheral nervous system disorders  
and methods for screening the compds.)

IT Hypertension  
(intracranial; Methods and ion-dependent cotransporter antagonist  
compds. for treating central and peripheral nervous system disorders  
and methods for screening the compds.)

IT Neuroglia  
(ion-dependent cotransporter antagonist highly active in; Methods and  
compds. for treating central and peripheral nervous system disorders  
and methods for screening the compds.)

IT Diuretics  
(loop, in combination with anti-seizure compn.; Methods and  
ion-dependent cotransporter antagonist compds. for treating central and  
peripheral nervous system disorders and methods for screening the  
compds.)

IT Headache  
(migraine; Methods and ion-dependent cotransporter antagonist compds.  
for treating central and peripheral nervous system disorders and  
methods for screening the compds.)

IT Toxicity  
(neurotoxicity; Methods and ion-dependent cotransporter antagonist  
compds. for treating central and peripheral nervous system disorders  
and methods for screening the compds.)

IT Nervous system  
(peripheral, disorders; Methods and ion-dependent cotransporter  
antagonist compds. for treating central and peripheral nervous system  
disorders and methods for screening the compds.)

IT Epilepsy  
(status epilepticus; Methods and ion-dependent cotransporter antagonist  
compds. for treating central and peripheral nervous system disorders  
and methods for screening the compds.)

IT Brain, disease  
(stroke; Methods and ion-dependent cotransporter antagonist compds. for  
treating central and peripheral nervous system disorders and methods  
for screening the compds.)

IT Nerve  
(toxicity; Methods and ion-dependent cotransporter antagonist compds.  
for treating central and peripheral nervous system disorders and  
methods for screening the compds.)

IT Head  
(trauma; Methods and ion-dependent cotransporter antagonist compds. for  
treating central and peripheral nervous system disorders and methods  
for screening the compds.)

IT Pain  
(treatment; Methods and compds. for treating central and peripheral

nervous system disorders and methods for screening the compds.)

IT 50-06-6, Phenobarbital, biological studies  
(as anti-seizure compn., in combination with ion-dependent cotransporter; Methods and compds. for treating central and peripheral nervous system disorders and methods for screening the compds.)

IT 54-31-9  
(in combination with anti-seizure compn.; Methods and ion-dependent cotransporter antagonist compds. for treating central and peripheral nervous system disorders and methods for screening the compds.)

IT 50-11-3, Metharbital 50-12-4, Mephentyoin 57-41-0, Phenytoin 63-98-9, Phenacemide 67-52-7D, 2,4,6(1H,3H,5H)-Pyrimidinetrione, derivs. 76-74-4, Pentobarbital 76-75-5, Thiopental 77-41-8, Methsuximide 77-67-8, Ethosuximide 86-34-0, Phensuximide 86-35-1, Ethotoin 99-66-1 115-38-8, Mephobarbital 115-67-3, Paramethadione 125-33-7, Primidone 125-84-8, Aminoglutethimide 127-48-0, Trimethadione 298-46-4, Carbamazepine 439-14-5, Diazepam 501-68-8 1622-61-3, Clonazepam 2078-54-8, Propofol 7772-37-4, Phethenylate 22316-47-8, Clobazam 23887-31-2, Clorazepate 25451-15-4, Felbamate 28721-07-5, Oxcarbazepine 59467-70-8, Midazolam 60142-96-3, Gabapentin 68291-97-4, Zonisamide 68506-86-5, Vigabatrin 84057-84-1, Lamotrigine 93390-81-9, Fosphenytoin 97240-79-4, Topiramate 102767-28-2, Levetiracetam 103628-46-2, Sumatriptan 115103-54-3, Tiagabine 132014-88-1 157971-06-7, GYK152466  
(in combination with ion-dependent cotransporter antagonist; Methods and compds. for treating central and peripheral nervous system disorders and methods for screening the compds.)

IT 7440-09-7, Potassium, biological studies 7440-23-5, Sodium, biological studies 16887-00-6, Chloride, biological studies  
(sodium potassium chloride cotransporter antagonist; Methods and ion-dependent cotransporter antagonist compds. for treating central and peripheral nervous system disorders and methods for screening the compds.)

RN 50-06-6  
RN 54-31-9  
RN 50-11-3  
RN 50-12-4  
RN 57-41-0  
RN 63-98-9  
RN 67-52-7D  
RN 76-74-4  
RN 76-75-5  
RN 77-41-8  
RN 77-67-8  
RN 86-34-0  
RN 86-35-1  
RN 99-66-1  
RN 115-38-8  
RN 115-67-3  
RN 125-33-7  
RN 125-84-8  
RN 127-48-0  
RN 298-46-4  
RN 439-14-5  
RN 501-68-8  
RN 1622-61-3  
RN 2078-54-8  
RN 7772-37-4  
RN 22316-47-8  
RN 23887-31-2  
RN 25451-15-4  
RN 28721-07-5  
RN 59467-70-8  
RN 60142-96-3  
RN 68291-97-4

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| RN | 68506-86-5  |
| RN | 84057-84-1  |
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| RN | 97240-79-4  |
| RN | 102767-28-2 |
| RN | 103628-46-2 |
| RN | 115103-54-3 |
| RN | 132014-88-1 |
| RN | 157971-06-7 |
| RN | 7440-09-7   |
| RN | 7440-23-5   |
| RN | 16887-00-6  |

L9 ANSWER 21 OF 26 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN  
ACCESSION NUMBER: 2000:196849 BIOSIS  
DOCUMENT NUMBER: PREV200000196849  
TITLE: Sodium pump activity, not glial spatial buffering, clears potassium after epileptiform activity induced in the dentate gyrus.  
AUTHOR(S): Xiong, Zhi-Qi; Stringer, Janet L. (1)  
CORPORATE SOURCE: (1) Dept. of Pharmacology, Baylor College of Medicine, One Baylor Plaza, Houston, TX, 77030 USA  
SOURCE: Journal of Neurophysiology (Bethesda), (Marcj, 2000) Vol. 83, No. 3, pp. 1443-1451.  
ISSN: 0022-3077.  
DOCUMENT TYPE: Article  
LANGUAGE: English  
SUMMARY LANGUAGE: English

AB A number of mechanisms have been proposed to play a role in the regulation of activity-dependent variations in extracellular potassium concentration ((K<sup>+</sup>)<sub>o</sub>). We tested possible regulatory mechanisms for (K<sup>+</sup>)<sub>o</sub> during spontaneous recurrent epileptiform activity induced in the dentate gyrus of hippocampal slices from adult rats by perfusion with 8 mM potassium and 0-added calcium medium in an interface chamber. Local application of tetrodotoxin blocked local (K<sup>+</sup>)<sub>o</sub> changes, suggesting that potassium is released and taken up locally. Perfusion with barium or cesium, **blockers** of the inward rectifying potassium channel, did not alter the baseline (K<sup>+</sup>)<sub>o</sub>, the ceiling level of (K<sup>+</sup>)<sub>o</sub> reached during the burst, or the rate of (K<sup>+</sup>)<sub>o</sub> recovery after termination of the bursts. Decreasing gap junctional conductance did not change the baseline (K<sup>+</sup>)<sub>o</sub> or the half-time of recovery of the (K<sup>+</sup>)<sub>o</sub> after the bursts but did cause a decrease in the ceiling level of (K<sup>+</sup>)<sub>o</sub>. Perfusion with furosemide, which will block cation/chloride **cotransporters**, or perfusion with low chloride did not change the baseline (K<sup>+</sup>)<sub>o</sub> or the half-time of recovery of the (K<sup>+</sup>)<sub>o</sub> after the bursts but did increase the ceiling level of (K<sup>+</sup>)<sub>o</sub>. Bath or local application of ouabain, a Na<sup>+</sup>/K<sup>+</sup>-ATPase **inhibitor**, increased the baseline (K<sup>+</sup>)<sub>o</sub>, slowed the rate of (K<sup>+</sup>)<sub>o</sub> recovery, and induced spreading **depression**. These findings suggest that potassium redistribution by glia only plays a minor role in the regulation of (K<sup>+</sup>)<sub>o</sub> in this model. The major regulator of (K<sup>+</sup>)<sub>o</sub> in this model appears to be uptake via a Na<sup>+</sup>/K<sup>+</sup>-ATPase, most likely neuronal.

9 ANSWER 14 OF 26 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN

ACCESSION NUMBER: 1998:89782 BIOSIS

DOCUMENT NUMBER: PREV199800089782

TITLE: Interaction between Na<sup>+</sup>/phosphate-cotransporter and the adrenoceptors in myocardial **depression**.

AUTHOR(S): Onwochei, Michael O. (1); Ofori, Abena O.; Agodoa, Irene L.

CORPORATE SOURCE: (1) Dep. Pharmacol. and Therapeutics, Med. Coll. Ohio, 3000 Arlington Ave., P.O. Box 10008, Toledo, OH 43699-0008 USA

SOURCE: Journal of Cardiovascular Pharmacology, (Jan., 1998) Vol. 31, No. 1, pp. 10-17.

ISSN: 0160-2446.

DOCUMENT TYPE: Article

LANGUAGE: English

AB The primary objective of this study was to test the hypothesis that an increase in the alpha1-adrenoceptor tone would potentiate the myocardial biphasic contractile response to inorganic phosphate (Pi, the substrate of Na/Pi-**cotransporter** (NP)). A second aim was to determine whether activation of alpha1-adrenoceptor is necessary for the NP-mediated increase in myocardial contractility (+dP/dt). Earlier study from this laboratory showed that high concentration of Pi (10 mM) produces a biphasic contractile response: initial increase in +dP/dt was followed by decline. In another study, Pi (3.5 mM) potentiated phenylephrine (PHE)-induced increase in +dP/dt. The alpha1-adrenoceptor was not blocked in these studies, and it can still be activated by the electrical stimulation of the sympathetic nerve terminals to the heart. Additionally, alpha1-adrenoceptor-activated increases in the activity of NP have been reported in numerous studies in noncardiac tissues and cell lines; therefore it is not clear whether Pi-induced increase in +dP/dt occurs only in the presence of alpha1-adrenoceptor activation. This study was performed by using isolated perfused rat heart in the condition of controlled extracellular calcium activity (0.72 mM); fixed preload (15 mm Hg); and constant heart rate (280 beats/min) and coronary flow (8 ml/min). The electronically differentiated value of the left ventricular pressure (LVP) signal was used as an index of myocardial contractility. The data show that activation of the alpha1-adrenoceptor is not necessary for the Pi-induced increase in +dP/dt (i.e., NP-mediated increase in +dP/dt has both the alpha1-adrenoceptor-dependent and alpha1-adrenoceptor-independent components. The interaction between alpha1-adrenoceptor agonist (PHE) and Pi (10 mM) did not produce a biphasic myocardial contractile response in the presence of propranolol. Because our earlier data on myocardial biphasic contractile response to 10 mM Pi was obtained when neither the beta- nor the alpha-adrenoceptor was blocked, we carried out more studies to see whether beta-adrenoceptor plays a role in this Pi-induced biphasic response. When both the alpha- and beta-adrenoceptors were activated with norepinephrine (NE), myocardial **depression** by high Pi concentration was markedly potentiated. This myocardial **depression** did not occur in the presence of phosphonoformate, a selective **inhibitor** of NP. It also did not occur when alpha1-adrenoceptor was blocked. Our data suggest that alpha1- and beta-adrenoceptors do not interact with the cardiac NP to potentiate the Pi-induced biphasic contractile response, but they interact in a manner that potentiates Pi-induced myocardial **depression**.

L9 ANSWER 10 OF 26 USPATFULL on STN

ACCESSION NUMBER: 2003:100059 USPATFULL

TITLE: Co-administration of melanocortin receptor agonist and phosphodiesterase inhibitor for treatment of cyclic-AMP associated disorders

INVENTOR(S): Macor, John E., Guilford, CT, UNITED STATES  
Carlson, Kenneth E., West Windsor, NJ, UNITED STATES

|                     | NUMBER        | KIND | DATE          |
|---------------------|---------------|------|---------------|
| PATENT INFORMATION: | US 2003069169 | A1   | 20030410      |
| APPLICATION INFO.:  | US 2002-90258 | A1   | 20020304 (10) |

|                       | NUMBER          | DATE          |
|-----------------------|-----------------|---------------|
| PRIORITY INFORMATION: | US 2001-273206P | 20010302 (60) |
|                       | US 2001-273291P | 20010302 (60) |
|                       | US 2001-289719P | 20010509 (60) |

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: STEPHEN B. DAVIS, BRISTOL-MYERS SQUIBB COMPANY, PATENT DEPARTMENT, P O BOX 4000, PRINCETON, NJ, 08543-4000

NUMBER OF CLAIMS: 13

EXEMPLARY CLAIM: 1

NUMBER OF DRAWINGS: 1 Drawing Page(s)

LINE COUNT: 2497

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Co-administration of a melanocortin receptor agonist, particularly an MC-1R or MC-4R agonist, and a cAMP phosphodiesterase inhibitor is described for modulating levels of cyclic adenoise 3',5' monophosphate (cAMP) in a mammal. The inventive co-administration is useful in the treatment of diseases affected by activity of cAMP-PDE, including without limitation, inflammatory bowel disease, irritable bowel syndrome, rheumatoid arthritis, osteoarthritis, pancreatitis, psoriasis, **migraine**, Alzheimer's Disease, Parkinson's disease, transplant rejection, asthma, acute respiratory distress syndrome, chronic obstructive pulmonary disease, stroke, and neurodegeneration of, and consequences of traumatic brain injury.



L9 ANSWER 9 OF 26 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED.  
on STN

ACCESSION NUMBER: 2001010115 EMBASE  
TITLE: The effect of sertraline on routine blood chemistry values.  
AUTHOR: Catalano M.C.; Catalano G.; Kanfer S.N.; Toner L.C.; Stock  
S.L.; Taylor W.D.  
CORPORATE SOURCE: G. Catalano, South Florida Psychiat. Center Univ., 3515  
East Fletcher Ave., Tampa, FL 33613, United States  
SOURCE: Clinical Neuropharmacology, (2000) 23/5 (267-270).  
Refs: 26  
ISSN: 0362-5664 CODEN: CLNEDB  
COUNTRY: United States  
DOCUMENT TYPE: Journal; Article  
FILE SEGMENT: 008 Neurology and Neurosurgery  
032 Psychiatry  
037 Drug Literature Index  
038 Adverse Reactions Titles  
LANGUAGE: English  
SUMMARY LANGUAGE: English

AB Sertraline is an antidepressant of the selective serotonin reuptake inhibitor (SSRI) class. Although SSRIs are believed to have a milder side effect profile than the tricyclic antidepressants, there are some potentially serious side effects. These include hyponatremia, which has been seen with each of the SSRIs. We reviewed the charts of 246 patients treated with sertraline at a veterans' hospital. We obtained values for each patient's basic chemistry panel (**sodium, potassium, chloride**, glucose, carbon dioxide, blood urea nitrogen, and creatinine) before and after institution of sertraline therapy. We studied the patients' ages and sertraline doses to see if there was a relationship between any laboratory value changes and these variables. We found no relationship between maximum sertraline dose, age, and changes in routine blood chemistry results with the exception of a small (0.5%) contribution of maximum sertraline dose to variance in serum creatinine levels. Sertraline therapy was not noted to cause any significant changes in serum sodium levels.

L9 ANSWER 6 OF 26 USPATFULL on STN

ACCESSION NUMBER: 2002:122675 USPATFULL  
TITLE: Benzamide ligands for the thyroid receptor  
INVENTOR(S): Ryono, Denis E., Princeton, NJ, United States  
PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, Princeton, NJ, United States (U.S. corporation)

|                     | NUMBER         | KIND | DATE         |
|---------------------|----------------|------|--------------|
| PATENT INFORMATION: | US 6395784     | B1   | 20020528     |
| APPLICATION INFO.:  | US 2001-871347 |      | 20010531 (9) |

|                       | NUMBER                                 | DATE          |
|-----------------------|--|---------------|
| PRIORITY INFORMATION: | US 2000-210102P                        | 20000607 (60) |
| DOCUMENT TYPE:        | Utility                                |               |
| FILE SEGMENT:         | GRANTED                                |               |
| PRIMARY EXAMINER:     | Killos, Paul J.                        |               |
| LEGAL REPRESENTATIVE: | Kilcoyne, John M.                      |               |
| NUMBER OF CLAIMS:     | 29                                     |               |
| EXEMPLARY CLAIM:      | 1                                      |               |
| NUMBER OF DRAWINGS:   | 0 Drawing Figure(s); 0 Drawing Page(s) |               |
| LINE COUNT:           | 982                                    |               |

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB New thyroid receptor ligands are provided which have the general formula  
##STR1##

in which:

X is --O--, --S--, --CH.sub.2--, --CO--, or --NH--;

R.sub.1 is halogen, trifluoromethyl, or alkyl of 1 to 6 carbons or cycloalkyl of 3 to 7 carbons;

R.sub.2 and R.sub.3 are the same or different and are hydrogen, halogen, alkyl of 1 to 4 carbons or cycloalkyl of 3 to 6 carbons, at least one of R.sub.2 and R.sub.3 being other than hydrogen;

R.sub.4 is methyl, ethyl, n-propyl or trifluoromethyl;

R.sub.5 is hydrogen or lower alkyl;

R.sub.6 is carboxylic acid, or esters or prodrugs;

R.sub.7 is hydrogen or an alkanoyl or an aroyl.

In addition, a method is provided for preventing, inhibiting or treating a disease associated with metabolism dysfunction or which is dependent upon the expression of a T.sub.3 regulated gene, wherein a compound as described above is administered in a therapeutically effective amount. Examples of such diseases associated with metabolism dysfunction or are dependent upon the expression of a T.sub.3 regulated gene include obesity, hypercholesterolemia, atherosclerosis, cardiac arrhythmias, **depression**, osteoporosis, hypothyroidism, goiter, thyroid cancer as well as glaucoma, congestive heart failure and skin disorders.

L9 ANSWER 4 OF 26 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN  
ACCESSION NUMBER: 2003:71074 BIOSIS  
DOCUMENT NUMBER: PREV200300071074  
TITLE: Methods and compositions for treating conditions of the  
central and peripheral nervous systems using non-synaptic  
mechanisms.  
AUTHOR(S): Hochman, Daryl W.  
ASSIGNEE: Cytoscan Sciences LLC, Seattle, WA, USA  
PATENT INFORMATION: US 6495601 December 17, 2002  
SOURCE: Official Gazette of the United States Patent and Trademark  
Office Patents, (Dec. 17 2002) Vol. 1265, No. 3, pp. No  
Pagination. <http://www.uspto.gov/web/menu/patdata.html>.  
e-file.  
ISSN: 0098-1133.  
DOCUMENT TYPE: Patent  
LANGUAGE: English

AB The present invention relates to methods and compositions for treating  
selected conditions of the central and peripheral nervous systems  
employing non-synaptic mechanisms. More specifically, one aspect of the  
present invention relates to methods and materials for treating seizure  
and seizure disorders, epilepsy, status epilepticus, **migraine**,  
spreading **depression**, intracranial hypertension; for treating  
the pathophysiological effects of head trauma, stroke, ischemia and  
hypoxia; for treating or protecting from the pathophysiological effects of  
neurotoxic agents such as ethanol; and for treating neurophysciatric  
disorders and central nervous system edema by administering agents that  
modulate ionic concentrations and/or ionic gradients in the brain,  
particularly ion-dependent or cation-chloride **cotransporter**  
**antagonists**. Ion-dependent cotransport **antagonists** and  
combinations of such compositions with other agents for treating various  
conditions are disclosed. The present invention also relates to methods  
and compositions for treating pain by administering ion-dependent  
**cotransporter antagonists**. Methods and compositions for  
enhancing cortical function, for example, in centers of cognition,  
learning and memory, by administering ion-dependent **cotransporter**  
agonists are disclosed. Methods and systems for screening drug candidate  
compounds for desired activities using in vitro and in vivo systems are  
disclosed.

L9 ANSWER 1 OF 26 CAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2000:441913 CAPLUS

DOCUMENT NUMBER: 133:68975

TITLE: Methods and ion-dependent **cotransporter antagonist** compounds for treating central and peripheral nervous system disorders and methods for screening the compounds

INVENTOR(S): Hochman, Daryl

PATENT ASSIGNEE(S): Cytoscan Sciences L.L.C., USA

SOURCE: PCT Int. Appl., 90 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

| PATENT NO.             | KIND   | DATE   | APPLICATION NO. | DATE       |
|------------------------|--|--|-----------------|------------|
| WO 2000037616          | A1   | 20000629   | WO 1999-US30806 | 19991222   |
| W:                     | AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM   |  |                 |            |
| RW:                    | GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG   |  |                 |            |
| CA 2356460             | AA   | 20000629   | CA 1999-2356460 | 19991222   |
| EP 1141251             | A1   | 20011010   | EP 1999-967584  | 19991222   |
| R:                     | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO   |  |                 |            |
| JP 2002533353          | T2   | 20021008   | JP 2000-589672  | 19991222   |
| PRIORITY APPLN. INFO.: |  |  | US 1998-113620P | P 19981223 |
|                        |  |  | US 1999-326244  | A 19990604 |
|                        |  |  | WO 1999-US30806 | W 19991222 |
| AB                     | Methods and compns. for treating selected conditions of the central and peripheral nervous systems employing non-synaptic mechanisms are described. Examples of the selected conditions are seizure, epilepsy, status epilepticus, <b>migraine</b> , spreading <b>depression</b> , intracranial hypertension; pathophysiol. effects of head trauma, stroke, ischemia and hypoxia; pathophysiol. effects of neurotoxic agents such as ethanol; neuropsychiatric disorders, and central nervous system edema. Treatment comprises administering agents that modulate ionic concns. and/or ionic gradients in the brain, particularly ion-dependent or cation-chloride <b>cotransporter antagonists</b> . Electrolyte cotransport antagonists (e.g., furosemide) and combinations of such compns. with other agents are disclosed. Methods and systems for screening drug candidate compds. for desired activities using in vitro and in vivo systems are also described. |  |                 |            |
| REFERENCE COUNT:       | 7  | THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT |                 |            |

L9 ANSWER 2 OF 26 CAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2002:488246 CAPLUS

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TITLE: Methods and compositions using ion-dependent cotransporter modulators for treating conditions of the central and peripheral nervous systems using non-synaptic mechanisms

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PATENT ASSIGNEE(S): Cytoscan Sciences L.L.C., USA

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| US 2002082252          | A1   | 20020627 | US 2002-56528   | 20020123    |
| US 6495601             | B1   | 20021217 | US 1999-470637  | 19991222    |
| PRIORITY APPLN. INFO.: |      |          | US 1998-113620P | P 19981223  |
|                        |      |          | US 1999-470637  | A2 19991222 |
|                        |      |          | US 2001-263830P | P 20010123  |

AB The invention discloses methods and compns. for treating selected conditions of the central and peripheral nervous systems employing non-synaptic mechanisms. More specifically, one aspect of the invention provides methods and materials for treating seizure and seizure disorders, epilepsy, status epilepticus, **migraine**, spreading **depression**, intracranial hypertension; for treating the pathophysiol. effects of head trauma, stroke, ischemia and hypoxia; for treating or protecting from the pathophysiol. effects of neurotoxic agents such as ethanol; and for treating neurophysciatric disorders and central nervous system edema by administering agents that modulate ionic concns. and/or ionic gradients in the brain, particularly ion-dependent or cation-chloride **cotransporter antagonists**. Electrolyte cotransport antagonists and combinations of such compns. with other agents for treating various conditions are disclosed. The invention also discloses methods and compns. for treating pain by administering ion-dependent **cotransporter antagonists**. Methods and compns. for enhancing cortical function, e.g. in centers of cognition, learning, and memory, by administering ion-dependent cotransporter agonists are disclosed.

L9 ANSWER 3 OF 26 USPATFULL on STN